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Seizure control and biochemical profile on the ketogenic diet in young children with refractory epilepsy—Indian experience

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ABSTRACT

Aim: This study evaluated the efficacy and tolerability of the ketogenic diet (KD) in young Indian children with refractory epilepsy. The changes in biochemical and lipid profile with KD were also assessed.
Methods: Children aged 6 months to 5 years who had daily seizures (or at least 7 seizures/week) despite the appropriate use of at least three antiepileptic drugs were enrolled. KD was introduced using a non-fasting gradual initiation protocol. Seizure frequency, biochemical profile (liver and kidney function tests, fasting lipid profile, and spot urinary calcium–creatinine ratio) and adverse effects were recorded. Patients continuing KD were followed up for a minimum period of 12 months.
Results: Twenty-seven children were enrolled. Non-fasting gradual KD initiation was well tolerated. Eighty-eight percent remained on KD at 3 months, 55% remained on KD at 6 months, and 37% remained on it at 1 year. Intention-to-treat analysis revealed that 48% (13 of 27) had >50% reduction in seizures, and four children (15 %) were seizure free at 6 months. At 1 year, 37% had >50% reduction in seizures and five children (18.5%) were seizure free. Adverse effects included constipation (74%), weight loss (14.8%), edema due to hypo-albuminemia (7.4%) and renal stones (3.7%). Biochemical profile did not reveal significant changes over time, except for reduced serum albumin and increased spot urinary calcium–creatinine ratio.
Conclusion: KD is an effective and well-tolerated treatment option in young Indian children with refractory epilepsy. However, careful ongoing medical supervision is needed.

1. Introduction

Several severe catastrophic epilepsies such as West syndrome, Lennox-Gastaut syndrome and myoclonic-astatic epilepsy present in infants and young children. Seizures in these disorders are difficult to control; sometimes only at the expense of multiple and toxic levels of antiepileptic medications. Epilepsy surgery is not a very beneficial option in this group. The shortcomings of antiepileptic drug therapy and epilepsy surgery have led to the need for alternative treatments. Ketogenic diet (KD) is a medically supervised high fat, low carbohydrate diet that maintains a chronic state of ketosis while providing proteins and calories for adequate growth.[1] The reported effectiveness of KD matches or exceeds that of antiepileptic drugs (AED) in many cases. Past studies have shown that at least 40–50% of children with epilepsy have more than a 50% reduction in seizures when on KD.[1–8]

There is paucity of data on the usefulness of KD in Indian children with epilepsy. Perceived difficulties include doubtful acceptability in a predominantly vegetarian population, unavailability of labelled foods, and unfamiliarity of dieticians with KD. Therefore, this study was planned to assess the feasibility, efficacy, and tolerability of KD in young Indian children with refractory epilepsy. We also assessed the changes in biochemical and lipid profile with KD.

2. Methods

2.1. Patient selection

This prospective open label, uncontrolled, study was conducted in the Pediatric Department of a tertiary care hospital between September 2006 and April 2008. Ethical approval by the institutional ethics committee was obtained. Written informed consent was obtained from the parents. Children aged 6 months to 5 years who had at least 1 seizure/day or 7 seizures/week despite the appropriate use of at least three antiepileptic drugs (AED) including one newer AED were enrolled. Children with known or suspected inborn errors of metabolism, systemic illness, or surgically remediable causes of epilepsy were excluded.

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2.2. Pre-diet preparation

Each child underwent detailed history and examination. Seizure type, frequency, age at onset, perinatal details, family history, developmental status and treatment history were noted. Medications were changed to carbohydrate free preparations, wherever available. Corticosteroids or ACTH were tapered off 2 weeks before starting the diet. The following investigations were obtained at baseline: electroencephalography (EEG), blood urea, serum creatinine, liver function tests (serum bilirubin, serum glutamate oxaloacetate transaminase [SGOT], serum glutamate pyruvate transaminase [SGPT] and serum albumin), fasting lipid profile including total cholesterol, serum triglycerides, low density lipoprotein [LDL], high density lipoprotein [HDL], and very low density lipoprotein [VLDL] and urinary spot calcium–creatinine ratios.

2.3. KD initiation

The children were admitted to the hospital for KD initiation using the non-fasting gradual initiation protocol described by Bergqvist et al.[9] KD was started with a full calorie, ketogenic ratio (ratio of fat:protein + carbohydrate) by weight of 1:1. This was built up over a period of 4 days to 3:1 in children younger than 18 months, and 4:1 in children older than 18 months. The recipes were planned in-house and calculated considering the families and the child's preferences and cultural taboos. Diets were based on Indian recipes and prepared with common locally available foods. Blood sugar was monitored 8 hourly, and urine ketones were checked by Dipstick at every void. The child was discharged by the fourth or fifth day. The AED were continued unchanged.

While the child was hospitalized, training about the calculation of meals, weighing of foods, and the rationale behind the diet was re-inforced. Parents were given diet plans and recipes to be made at home. Each child also received a sugar-free, fat soluble vitamin supplement and calcium supplementation.

2.4. Follow up

Patients were followed up at 1, 2, 3, 6 months and 1 year after KD initiation. Seizure frequency was checked according to parental reports and seizure diaries. The seizure control was categorized as seizure free, >90% seizure reduction, 50–90% seizure reduction, <50% seizure reduction or increase in seizures. Compliance with the diet was checked by parental records of daily urine ketones chart. Adverse effects were noted. The biochemical profile including a fasting lipid profile, and urinary spot calcium–creatinine ratios were tested at each follow up visit. Oral potassium citrate supplementation was started in children with urinary spot calcium creatinine ratio more than 0.2. EEG was obtained at 3 months, 6 months and 12 months after diet initiation.

2.5. Statistical analysis

Data was analysed using SPSS software version 15. The non-parametric two way analysis of variance, i.e. Friedman test was applied to see any change over time for continuous variables. For categorical tests, Chi square test was applied. The level of significance was taken as 0.05.

3. Results

During the study period, parents of 27 of the 41 children found eligible for inclusion were willing for trial (Fig. 1). In 14 patients; the parents were not willing for KD trial. The reasons cited were: feeling that child would find diet too restrictive (6), financial constraints (2), unwilling for hospital admission (2), mother having too much work at home, and unable to spare time for weighing and preparation of meals (2), staying far-off and unwilling for regular follow up (2). Out of the 27 patients included in the trial, 18 were vegetarian. Apart from those with infantile spasms, seizure frequency ranged from 5 to 100/day. Most patients suffered from mixed seizure types (Table 1). All the patients suffered from generalized epilepsy syndromes: the most frequently encountered types being Lennox-Gastaut syndrome (14), West syndrome (6) and myoclonic astatic epilepsy (4). In three patients, the epilepsy syndrome could not be classified, but the predominant seizure type was myoclonic. Multiple AED had been tried (median 5 AED, range 3–11).

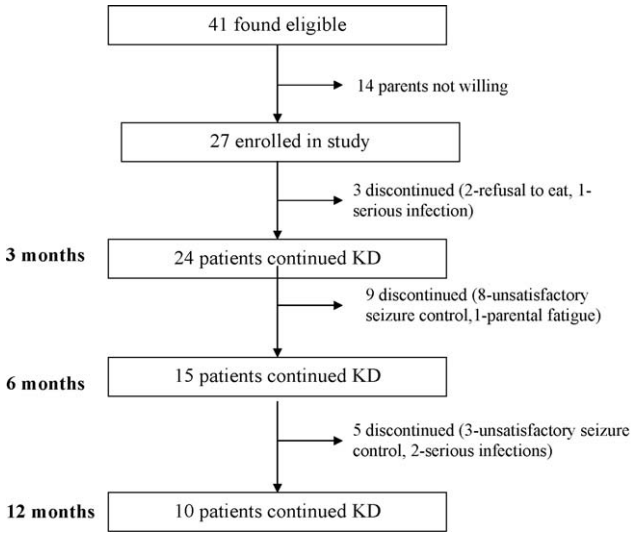

Fig. 1. Flow of patients in the study.

KD initiation was well tolerated. The most common side effect was vomiting, noted in 75% of the patients. No patient developed

Table 1
Demographic and clinical characteristics of the study population ($n = 27$).

Characteristic	Median (range)
Age at first seizure	4 months (15 days to 36 months)
Age at start of diet	2.5 years (9 months to 5 years)
AED tried (no.) before KD institution	5 (3–11)
Characteristic	**Number (%)**
Seizure type[a]	
Myoclonic	17 (62.9%)
Atypical absence	15 (55.5%)
Atonic	7 (25.9%)
Generalized tonic	18 (66.6%)
Infantile spasms	6 (22.2%)
Partial	2 (7.4%)
Generalized tonic clonic	3 (11.1%)
Epilepsy syndrome	
Lennox Gastaut syndrome	14 (51.8%)
West syndrome	6 (22.2%)
Myoclonic astatic epilepsy	4 (14.8%)
Symptomatic generalized epilepsy (unclassified)	3 (11.1%)
Co-morbidity	
Development delay	27 (100%)
Cerebral palsy	17 (62.9%)
Vision impairment	5 (18.5%)
Hearing impairment	4 (14.8%)
Feeding difficulties	9 (33.3%)
Hyperactivity	6 (22.2%)

[a] Most children had mixed seizure types.

Table 2
Seizure frequency on follow up.

Time on diet	Number of patients	<50% reduction	50–90% reduction	>90% reduction	Seizure free	Increase
3 months	24	7 (25.9%)	9 (33.3%)	4 (14.8%)	3 (11.1%)	1 (3.7%)
6 months	15	2 (7.4%)	7 (25.9%)	2 (7.4%)	4 (14.8%)	Nil
12 months	10	Nil	3 (11.1%)	2 (7.4%)	5 (18.5%)	Nil

Table 3
Biochemical profile on ketogenic diet.

	Baseline (n = 27), mean [SD]	1 month (n = 27), mean [SD]	2 months (n = 26), mean [SD]	3 months (n = 24), mean [SD]	6 months (n = 15), mean [SD]	12 months (n = 10), mean [SD]	p-Value
Blood urea (mg/dl)	21.33 [7.17]	19.66 [4.00]	19.84 [5.14]	19.52 [3.92]	18.13 [2.44]	18.30 [2.86]	0.242
S. creatinine (mg/dl)	0.57 [0.12]	0.58 [0.10]	0.56 [0.11]	0.61 [0.08]	0.62 [0.12]	0.69 [0.09]	0.243
SGOT (IU/l)	42.51 [15.95]	52.07 [34.35]	47.96 [30.48]	51.65 [30.66]	43.53 [17.15]	38.70 [5.71]	0.577
SGPT (IU/l)	26.33 [10.59]	40.62 [28.05]	34.03 [16.43]	39.91 [23.22]	35.00 [15.03]	36.33 [10.23]	0.454
S. Albumin (g/dl)	4.11 [.34]	4.11 [0.42]	4.18 [0.30]	4.08 [0.35]	4.04 [0.33]	3.96 [0.30]	0.0453*
Urine spot cal–creat ratio (mg/dl)	0.09 [0.09]	0.12 [0.07]	0.19 [0.08]	0.12 [0.05]	0.11 [0.08]	0.13 [0.04]	0.035*

* Significant.

symptomatic hypoglycaemia. One child developed asymptomatic hypoglycaemia which improved after feeding.

The number of children remaining on KD at 3, 6, and 12 months; and the percentage achieving varying levels of seizure control are shown in Table 2. Six months after starting KD, 15 of the 27 children (55.5%) were still on the diet. Four children (14.8%) were seizure free and two (7.4%) had 90% or greater decrease in seizures. An additional seven children (25.9%) had a 50–90% decrease in seizures. Thus at 6 months, 13 children (48.1%) of this difficult-to-control seizure population achieved a >50% decrease in seizures. At 1 year after initiating KD, 10 of the initial patients (37%) remained on it. Five (18.5%) were seizure free, and two (7.4%) had a 90% or greater decrease in seizures. An additional three (11.1%) children had a 50–90% reduction in seizure frequency. Thus, 1 year after starting KD, 10 children (37%) had achieved a >50% reduction in seizure.

EEG revealed background improvement in the form of reduced slowing, better organization or resolution of hypsarrhythmia or its variants in eight children at 6 months, and seven children at 1 year after KD initiation. Paroxysmal abnormalities in the form of reduced or absent polyspikes, reduced multifocal sharp waves and spikes, reduced generalized spike wave activity and reduced or absent paroxysmal fast activity was noted in seven children at 6 months and six children at 12 months after starting the diet.

The biochemical profile of the patients at baseline and follow up is detailed in Table 3. There was no statistically significant difference in blood urea, serum creatinine, SGOT and SGPT. There was a statistically significant fall in serum albumin (p = 0.04) and increase in spot urinary calcium to creatinine ratio (p = 0.03). The mean lipid profile parameters at baseline and follow up are shown in Fig. 2. The change in lipid profile over time was not statistically significant.

Constipation was the most common adverse effect, noted in nearly three-fourths of the patients. Four children lost weight during the first 3 months after starting KD. This was managed by increasing the calorie intake. One child developed renal stones. Two children developed hypo-albuminemia and edema. This improved on increasing the daily protein allowance. There were no deaths on the KD during the study period. Three children developed severe intercurrent infections requiring mechanical ventilation and ICU stay.

Unsatisfactory seizure control was the most common reason for discontinuation (11 children). In three children, as described above, the KD was discontinued because of severe intercurrent illness requiring mechanical ventilation and PICU stay. In two children, parents discontinued the KD in less than 3 months

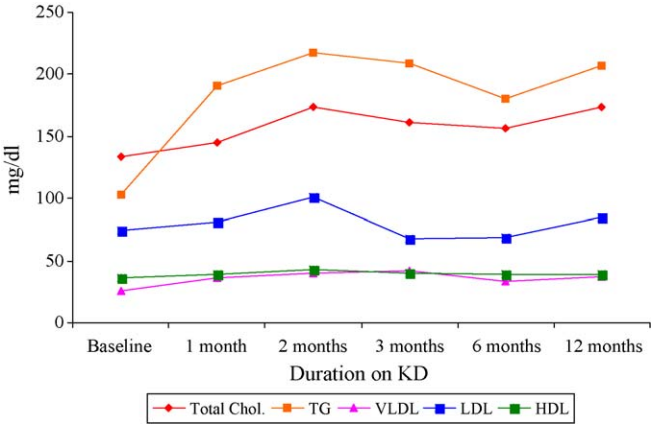

Fig. 2. Lipid profile in the study population at KD initiation and follow up.

duration, because of the child's refusal to eat; despite having 50–90% seizure control in one child.

4. Discussion

To our knowledge this is the first prospective study evaluating KD in Indian children with refractory epilepsy. Our results are comparable to previously published studies of KD.[1–15] Using intention-to-treat analysis, at 6 months on the diet, 14.8% were seizure free, and overall 48.1% had a 50% or greater reduction in seizures in our study. Our findings are comparable to the findings in a recent systematic review analyzing all studies of KD published between 1990 and 2005. Twenty-six studies were included in the review, with a total collective population of 972.[16] At 6 months, 15.6% patients had become seizure free while 33.0% were reported to have greater than 50% reduction in seizure frequency after commencing the diet.

In the present study, 10 children (37%) remained on KD for 1 year. As intention-to-treat analysis was used, the percentage of patients who had >50% seizure reduction at 12 months; i.e. 37%, was lower that at 6 months, i.e. 48.1%. The proportion of patients continuing KD for 1 year in previous studies has ranged from 7% to 56%.[16] Our results are comparable to those studies, where intention-to-treat analysis has been used to report outcomes. The long-term status of KD in Indian patients needs to be studied with large number of patients.

Although Indian diets are traditionally cereal-based and contain substantially less fat than traditional Western diets, KD was

nonetheless well tolerated. Indigenous recipes, keeping in mind cultural factors and food preferences (especially vegetarian food) were designed. Refusal to eat possibly because of unpalatibility was a cause for discontinuation in only two children. This is consistent with most studies on KD, which have demonstrated that KD is tolerated if it is effective in controlling seizures.[1–5]

Age, sex, seizure type and etiology has not been shown to predict response in previous studies.[1–5,10–15] There was no relationship between age, sex, etiology (cryptogenic versus symptomatic), or epilepsy syndrome and seizure control in the present study.

Blood urea, serum creatinine, SGOT and SGPT did not change significantly on the diet. Hassan et al., in a retrospective study did not find any abnormalities in routine biochemical testing when on KD.[4] There was a significant fall in mean serum albumin in the present study. Two patients had developed hypoproteinemia with pedal edema on the diet, which responded to increasing the protein intake from 1 g/kg/day to 2 g/kg/day. The recommendation in classic KD of protein intake of 1 g/kg/day seems to be less in the context of young Indian children. In children who developed serum albumin <3.5 g/dl, protein intake was increased to 1.5 g/kg/day. This increase of protein intake did not worsen the seizure control. Hypoproteinemia on KD has been described in isolated case reports,[17] but there are no studies with serial follow ups, like ours.

There was a significant rise in spot urinary calcium–creatinine ratio over time. Hypercalciuria occurs with the KD due to increased bone mineralization with acidosis as well as increased calcium excretion by the kidney. This leads to an increased risk for renal stones, which are reported in 3–10% of children on KD. Recently Sampath et al. evaluated the preventive use of potassium citrate in children on ketogenic diet in a retrospective cohort study.[18] Their results demonstrated that the use of oral potassium citrate significantly decreased the prevalence of stones (3.2% versus 10%, $p = 0.049$). The oral potassium citrate supplementation in children with urinary spot calcium creatinine ratio more than 0.2 in the present study limited the renal calculus prevalence to 3.7%.

The change in lipid profile over time in the present study was not statistically significant. Other authors have also described a similar trend.[12,13] Kwiterovich et al. however found increased lipid levels on KD.[19] In their study, after 6 months, the patients on KD had significantly increased mean plasma levels of total cholesterol, LDL, VLDL, and triglycerides. The long-term risks of this dyslipidemia are not clear.

Constipation was the most frequent side effect encountered. This has been the finding in other studies as well.[1–8,10–15] Weight loss at 3 months was noted in four children. A recent study examining the effect of KD on growth in 237 children revealed that the rate of weight gain decreased at 3 months, but remained constant for up to 3 years.[20] The calorie and protein intake need to be adjusted as per the weight gain of the child, as we did in our study.

The fact that three children developed severe intercurrent infections requiring mechanical ventilation and PICU stay is a cause for concern. Though most studies on KD have reported a few patients with severe infections or even deaths, these events have not been considered to be due to KD per se.[1–8,10–15] The deaths have been attributed to the fragile status of these children with refractory epilepsy, most of whom have severe global developmental delay and co-morbid cerebral palsy; which makes them more susceptible to serious infection. One study reported impaired neutrophil function in children on KD; however, this finding has not been evaluated or reported in further studies.[21]

5. Conclusion

KD is a feasible, well-tolerated and effective therapeutic option for young Indian children with refractory epilepsy. Biochemical profile did not reveal significant changes over time, except for reduced serum albumin and increased spot urinary calcium–creatinine ratio. However, KD is not without possible side effects and careful medical supervision is warranted.

Conflict of interest

None.

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